REMARKS

I. STATUS OF THE CLAIMS

After entry of this amendment, claims 1-25 and 40 are pending in the present application. Claim 9 has been canceled without prejudice to future prosecution. Claims 26-39 were previously withdrawn. Claim 40 has been allowed.

Claims 1, 5, 6, 10-12, and 14 have been amended. Claims 1 and 12 have been amended to clarify that the sRNAP is capable of entering into the cytoplasm of a cell and retains the enzymatic activity of the native RNA polymerase, *i.e.*, the ability to carry out template dependent synthesis of RNA. Support is found, for example, on page 15, lines 12-14; page 22, lines 20-21; and page 23, lines 12-15. Claims 5 and 6 have been amended to recite that the first IRES and second IRES are the same sequence or different sequences, respectively. Claim 10 has been amended to establish proper dependency and antecedent basis from claim 1. Claims 11 and 14 have been amended in accordance with the Examiner's suggestions.

II. OBJECTION TO THE SPECIFICATION

The Examiner has objected to the specification as missing trademark designations for Triton® X-100 and RiboQuant™ RPA. The specification has been amended to include the appropriate trademark designations.

The Examiner has further objected to the specification as containing incorrect labels for Figure 9. Applicants have amended the specification so that the labels for Figure 9 are consistent with the labeling in the drawings.

Accordingly, Applicants respectfully request withdrawal of these objections.

III. OBJECTION TO THE CLAIMS

The Examiner has objected to claims 19, 23, and 24 as containing the acronym "PEG" without a corresponding definition. In the Office Action, the Examiner indicates that the objection can be overcome by including the acronym in claim 14. *See*, Office Action at page 4. In order to expedite prosecution of the present case, Applicants have amended claim 14 to recite

a "polyethyleneglycol (PEG)-lipid conjugate." Thus, Applicants respectfully request withdrawal of this objection.

IV. REJECTION UNDER 35 U.S.C. § 101

The Examiner has rejected claim 11 under 35 U.S.C. § 101 as allegedly directed to non-statutory subject matter. In the Office Action, the Examiner indicates that recitation of an "isolated host cell" would be remedial. *See*, Office Action at page 5. In order to expedite prosecution of the present case, Applicants have amended claim 11 to recite an "isolated host cell." Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101.

V. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner has rejected claims 1-25 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description and as allegedly lacking enablement. Applicants respectfully traverse. Each of these rejections is addressed below in the order set forth by the Examiner.

A. Written Description

The present invention is directed to a genus of expression cassettes comprising nucleic acids encoding a secretable RNA polymerase (sRNAP) having a secretion domain, wherein the sRNAP has the following functional characteristics: (1) the ability of entering into a cell cytoplasm; and (2) retains the enzymatic activity of the native RNA polymerase, *i.e.*, the ability to carry out template dependent synthesis of RNA.

In making this aspect of the rejection, the Examiner acknowledges that individual support for every species of the claimed sRNAP fusion proteins is not required, but appears to allege that Applicants must disclose individual support for every species of secretion domain to demonstrate possession of the claimed expression cassettes. Specifically, the Examiner focuses on the secretion domain component of the claimed expression cassettes and their mechanism of cellular entry and alleges that, based on the large number of potential secretion domains, one of skill in the art cannot envisage all fusion constructs encoding sRNAPs. As such, the Examiner

concludes that the claimed expression cassettes are insufficiently described in the specification. To the extent this rejection applies to the currently pending claims, Applicants respectfully traverse.

As set forth in MPEP § 2163(II)(A)(3)(a)(ii), an adequate disclosure of a claimed genus depends on whether one of skill in the art would recognize that the Applicant was in possession of the necessary common features of the elements of the members of the genus. Possession can be shown by describing sufficient distinguishing characteristics (*see, e.g.*, MPEP § 2163(I), citing *Pfaff v. Wells Elecs., Inc.*, 525U.S. 55 48 USPQ2d 1641 (1998); *University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); and *Amgen Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, USPQ2d 1016 (Fed. Cir. 1991)). A functional description of known compounds in the specification may be a sufficient description of the identifying characteristics of a claimed genus. *See*, MPEP § MPEP § 2163(II)(A)(3)(a)(ii), citing *In re Smythe* 480 F.2d 1376, 178 USPQ 279 (CCPA 1973). Moreover, as held in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002), "[i]t is not correct . . . that all functional descriptions of genetic material fail to meet the written description requirement." In *Enzo*, the Federal Circuit, referring to the USPTO Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112 ¶1, "Written Description" Requirement (66 Fed. Reg. 1099 (January 5, 2001)) held that the written description requirement is satisfied by a disclosure of relevant identifying characteristics, including functional characteristics coupled with a disclosed correlation between that function and a structure that is "sufficiently known or disclosed." *Id.*

It is well settled that the disclosure of a single species may support a genus. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323, 326-27 (CCPA 1981); *In re Herschler*, 591 F.2d 693. 200 USPQ 711 (CCPA 1979). The Federal Circuit recently affirmed the holding of *In re Smythe* that species representative of genus claims are descriptive of such claims. *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609, 1615 (Fed. Cir. 2002).

Contrary to the Examiner's allegation, the disclosure of the functional characteristics of the presently claimed expression cassettes and the teachings of the instant specification are more than sufficient to demonstrate to one of skill in the art that Applicants were in possession of the invention as claimed. As recited in the claims and as acknowledged by

the Examiner, the sRNAP encoded by the expression cassettes must be able to enter the cytoplasm of a cell ***and*** carry out template dependent transcription of RNA. The specification describes numerous suitable secretion domain sequences including signal peptides and protein translocation domains (*see, e.g.*, page 5, line 3 through page 7, line 13; and page 23, line 23 through page 26, line 3) and sets forth assays to determine: (1) whether the sRNAP can enter into a cell (*see, e.g.*, page 22, line 30 through page 23, line 10); and (2) whether the sRNAP retains the enzymatic activity of the native RNA polymerase (*see, e.g.*, page 22, lines 20-29). Finally, as acknowledged by the Examiner, the specification provides a working example that describes ***two*** disparate species that are representative of the claimed genus of expression cassettes, *i.e.*, SP6-VP22-T7-RNAP and SP6-TAT-T7-RNAP (*see, e.g.*, Example 1 on pages 49-50). Each of the expression cassettes described encode sRNAPs that have the functional characteristics recited in the present claims, *i.e.*, sRNAPs that enter the cytoplasm of a cell ***and*** retain the ability to carry out template dependent synthesis of RNA. Thus, the working examples provide an unequivocal demonstration to one of skill in the art that Applicants were in possession of the presently claimed genus of expression cassettes.

The Examiner also alleges that one of skill in the art would have to be apprised of the particular mechanism by which each secretion domain facilitates cellular membrane traversal. Specifically, the Examiner focuses on the HIV-TAT secretion domain and alleges that sRNAPs having this secretion domain would only be able to enter a limited number of cell types because HIV-TAT requires cell surface heparan sulfate to facilitate membrane transduction. However, the claims do not recite any particular mechanism by which sRNAP enters the cytoplasm. Moreover, the specification discloses that HIV-TAT secretion domains can be used to deliver active proteins, including enzymes, to a diverse number of cell types (*see, e.g.,* page 25, lines 21-27). In fact, the HIV-TAT secretion domain, when fused to β-galactosidase, results in delivery of the biologically active fusion protein to ***all*** tissues in mice, including the brain (*see, e.g.,* Schwarze *et al.*, *Science*, 285:1569-1572 (1999), cited at page 25, lines 23-24). Thus, in view of the instant specification and the Schwarze *et al.* reference cited therein, one of skill in the art would appreciate that HIV-TAT secretion domains are translocation polypeptides that can

be used to deliver biologically active proteins across all cellular membranes and, accordingly, that Applicants were in possession of the presently claimed genus of expression cassettes.

In view of the foregoing remarks, the disclosure of the instant specification is more than adequate to demonstrate to one of skill in the art that Applicants had possession of the presently claimed genus of expression cassettes at the time of the application was filed. Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

B. Enablement

In making this aspect of the rejection, the Examiner acknowledges that the specification enables one of skill in the art to create the sRNAP fusion proteins SP6-VP22-T7-RNAP and SP6-TAT-T7-RNAP, but alleges that the specification does not enable one of skill in the art to practice the full scope of the claims without undue experimentation. In addition, the Examiner asserts that the only disclosed utility for the given claimed compositions is gene therapy. To the extent this rejection applies to the currently pending claims, Applicants respectfully traverse.

1. sRNAPs

Contrary to the Examiner's allegation, the specification clearly enables one of skill in the art to practice the full scope of the claims without undue experimentation. As recited in the claims and as acknowledged by the Examiner, the sRNAP encoded by the expression cassettes must be able to enter the cytoplasm of a cell ***and*** carry out template dependent transcription of RNA. The specification describes numerous suitable secretion domain sequences including signal peptides and protein translocation domains (*see, e.g.*, page 5, line 3 through page 7, line 13; and page 23, line 23 through page 26, line 3) and sets forth assays to determine: (1) whether the sRNAP can enter into a cell (*see, e.g.*, page 22, line 30 through page 23, line 10); and (2) whether the sRNAP retains the enzymatic activity of the native RNA polymerase (*see, e.g.*, page 22, lines 20-29). Finally, as acknowledged by the Examiner, the specification provides a working example that describes ***two*** disparate species that are representative of the claimed genus of expression cassettes, *i.e.*, SP6-VP22-T7-RNAP and SP6-

TAT-T7-RNAP (*see, e.g.*, Example 1 on pages 49-50). Each of the expression cassettes described encode sRNAPs that have the functional characteristics recited in the present claims, *i.e.*, sRNAPs that enter the cytoplasm of a cell ***and*** retain the ability to carry out template dependent synthesis of RNA. Thus, the disclosure of the specification, including the working examples, provides ample guidance for one of skill in the art to create sRNAP fusion proteins having the functional characteristics recited in the claims.

The Examiner also takes the position that secretion domains are unpredictable with respect to cellular membrane traversal and alleges that that one of skill in the art would have to be apprised of the particular mechanism by which each secretion domain facilitates cellular entry. Specifically, the Examiner focuses on the HIV-TAT secretion domain and alleges that sRNAPs having this secretion domain would only be able to enter a limited number of cell types because HIV-TAT requires cell surface heparan sulfate to facilitate membrane transduction. However, the claims do not recite any particular mechanism by which sRNAP enters the cytoplasm. Moreover, the specification discloses that HIV-TAT secretion domains can be used to deliver active proteins, including enzymes, to a diverse number of cell types (*see, e.g.*, page 25, lines 21-27). In fact, the HIV-TAT secretion domain, when fused to β-galactosidase, results in delivery of the biologically active fusion protein to ***all*** tissues in mice, including the brain (*see, e.g.*, Schwarze *et al.*, *Science*, 285:1569-1572 (1999), cited at page 25, lines 23-24). Thus, in view of the instant specification and the Schwarze *et al.* reference cited therein, one of skill in the art would appreciate that HIV-TAT secretion domains are translocation polypeptides that can be used to deliver biologically active proteins across all cellular membranes and, accordingly, that it would not be unpredictable for sRNAPs having HIV-TAT secretion domains to possess the functional characteristics recited in the present claims, *i.e.*, sRNAPs that enter the cytoplasm of a cell ***and*** retain the ability to carry out template dependent synthesis of RNA.

In view of the foregoing remarks, Applicants submit that the specification provides ample guidance for one of skill in the art to create sRNAP fusion proteins having the functional characteristics recited in the claims. Therefore, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

2. Gene therapy

With regard to the Examiner's allegation that the claims read on gene therapy, Applicants have canceled claim 9 and amended claim 10 to reflect that the nucleic acids of the present invention find use in both *in vitro* and *in vivo* applications. This is supported by the instant specification, which teaches that the product of interest can be a product that is purified and used as a pharmaceutical (an *in vitro* use) or a therapeutic product that is expressed in a subject suffering from disease (an *in vivo* use) (*see, e.g.,* page 14, lines 17-23).

A patentable composition needs only one enabled use. *See,* 35 U.S.C. § 101; *see also, Raytheon v. Roper*, 724 F.2d 951 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835 (1984). The MPEP explains that this use must be specific, substantial, and credible. *See*, MPEP § 2164.07. Here, the claimed compositions have at least one specific, substantial, and credible use, *i.e.,* they are useful for the high level expression of products of interest in cells, including mammalian cells. Based on this use, one of skill in the art would readily recognize that the claimed expression cassettes find use for both *in vitro* and *in vivo* high level expression of products of interest in cells, including mammalian cells.

The Examiner acknowledges that Applicants have demonstrated the use of the present nucleic acids in two distinct examples of *in vitro* transfection (*see, e.g.,* Examples 2-3 on pages 50-51 and Figures 2-3 and 6-7 of the specification). The *in vitro* uses of the present nucleic acids include high level expression of products of interest for use as research tools (*see, e.g., Integra LifeSciences v. Merck*, 331 F.3d 860, 867 (recognizing the legitimacy of patented research tools)), or for purification for subsequent use as a pharmaceutical.

"Where there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, a rigorous correlation is not necessary." MPEP § 2164.02, citing *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985). With regard to the *in vivo* use of the present nucleic acids, the specification teaches: (1) nucleic acids encoding products of interest (pages 33-37); (2) introduction of the present nucleic acids into cells, including mammalian cells (pages 38-41); (3) methods of expressing the present nucleic acids encoding a product of interest in cells, including mammalian cells (pages 41-42); (4) diseases suitable for treatment using the present nucleic acids (pages 42-48); and (5) administration of the present nucleic acids (pages

48-49). Based on the teachings in the specification and the state of the art at the time of filing of the present invention, one of skill in the art would readily recognize that the high level expression of a product of interest in two distinct mammalian cell types *in vitro* as demonstrated by Applicants shows a reasonable correlation for use of the present nucleic acids to express a product of interest in mammalian cells *in vivo*.

In view of the teachings in the specification, one of skill in the art would recognize that the present nucleic acids are enabled for the use of high level expression of products of interest in a cell, including a mammalian cell, either *in vitro* or *in vivo*.

Accordingly, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

VI. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner has rejected claims 5 and 6 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse.

In order to expedite prosecution of the present case, Applicants have amended claim 5 to recite that the first IRES and second IRES are the same sequence. Similarly, Applicants have amended claim 6 to recite that the first IRES and second IRES are different sequences. Support for these amendments is found throughout the specification as filed including, for example, on page 7, lines 14-28, which discloses a variety of viral and mammalian IRES sequences. As such, the specification is clear to one of skill in the art with respect to what constitutes the same IRES sequence or different IRES sequences. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

VII. REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-7 and 9-25 under 35 U.S.C. § 103(a) as allegedly obvious over Dalby *et al.* (U.S. Patent No. 6,773,920) in view of Deng *et al.* (*Gene*, 143:245-249 (1994)) and Mizuguchi *et al.* (*Mol. Ther.*, 1:376-382 (2000)). Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the

knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claim limitations. MPEP § 2143. *See also, In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998).

In the Office Action, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to combine the IRES taught by Deng *et al.* and Mizuguchi *et al.* with the vector taught by Dalby *et al.* since the combination would create an expression vector in which secretable RNA polymerase and high levels of a heterologous protein would be expressed (*see,* Office Action at page 16). In response, Applicants assert that the combination of references fails to teach all the elements of the claimed invention.

The present claims are directed to an expression cassette comprising:

(a) a eukaryotic promoter and a ***first*** RNA polymerase promoter operably linked to a nucleic acid encoding a secretable RNA polymerase (sRNAP), and a first internal ribosome entry site (IRES); and

(b) a ***second*** RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest and a second IRES.

Applicants assert that Dalby *et al.* does not teach or suggest an expression cassette comprising a ***first*** RNA polymerase promoter operably linked to a nucleic acid encoding a sRNAP and a ***second*** RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest. In contrast to the presently claimed invention, Dalby *et al.* discloses an expression cassette with only a ***first*** T7 promoter operably linked to a VP22 translocation polypeptide which can be operably linked to any product of interest (*see, e.g.,* Figures 5 and 6). However, Dalby *et al.* fails to teach or suggest an expression cassette comprising a ***second*** RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest, as required by the present claims.

Deng *et al.* and Mizuguchi *et al.* do not supply the teaching that is clearly lacking in Dalby *et al.* Specifically, Deng *et al.* teaches an autogene plasmid with only a ***first*** T7 promoter operably linked to a T7 RNA polymerase and encephalomyocarditis (EMC) untranslated sequence (*see, e.g.,* Figure 1A), but fails to teach or suggest an expression cassette

comprising a ***second*** RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest, as required by the present claims. Mizuguchi *et al.* teaches a bicistronic vector with a β-actin promoter operably linked to both a first gene and an IRES-dependent second gene (*see, e.g.,* Figure 1), but fails to teach or suggest an expression cassette comprising a ***first*** RNA polymerase promoter operably linked to a nucleic acid encoding a sRNAP and a ***second*** RNA polymerase promoter operably linked to a nucleic acid encoding a product of interest, as required by the present claims. Thus, the combination of references does not disclose or suggest all of the elements of the presently claimed invention.

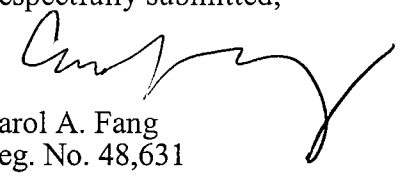
In view of the foregoing, the combined disclosures of Dalby *et al.*, Deng *et al.*, and Mizuguchi *et al.* do not render the claims obvious. Accordingly, the Examiner is respectfully requested to withdraw the present rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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